Third generation oral contraceptives and risk of venous thrombosis: meta-analysis
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Authors' objectives
To evaluate quantitatively articles that compared the effects of second- and third-generation oral contraceptives on the risk of venous thrombosis.

Searching
MEDLINE was searched for articles published from October 1995 to December 2000. The search terms used were 'third generation oral contraceptives', 'desogestrel', 'gestodene', 'thromboembolism' and 'venous thrombosis'. Additional references were retrieved from reviews, other articles of interest and experts in the field. Only articles written in the English language were included.

Study selection
Study designs of evaluations included in the review
Case-control studies (including nested case-control and population-based studies) and cohort study designs were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared second- and third-generation oral contraceptives were eligible for inclusion in the review. Third-generation contraceptives included those with specified (desogestrel and gestodene) and unspecified progestogen components. Second-generation contraceptives included levonorgestrel as a progestogen component.

Participants included in the review
Women taking oral contraceptives before 1995 in Western countries. Some had experienced venous thromboembolism and some had not, depending on the study design. The settings included hospitals, general practices, anticoagulant clinics and population-based settings.

Outcomes assessed in the review
In the case-control studies, a diagnosis of venous thrombosis or thromboembolism was an inclusion criterion for cases. Participants were then interviewed by questionnaire to identify oral contraceptive type. In cohort studies, the occurrence of venous thromboembolism was the outcome. Cases were considered confirmed when venous thrombosis was objectively diagnosed by ultrasound examination, plethysmography or venography. In all studies, sufficient data had to be provided to reconstruct 2x2 tables or to determine the relative risk and confidence intervals (CIs).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed. However, factors such as the definition of cases, source of funding and reporting of data were taken into account in the analysis.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. However, they do state that the data were systematically abstracted and ambiguous information was resolved through discussion between the three authors.

A study was included only once if there were multiple publications. If possible, 2x2 tables were extracted or...
recalculated. The data were extracted into the following categories: study type; setting; study period; study population; assessment of exposure; method of ascertainment; percentage with firm diagnosis; inclusion criteria; matching factors; control factors; and additional and extended studies.

Methods of synthesis
How were the studies combined?
First, the results of studies that compared the risk of venous thrombosis between third- and second-generation oral contraceptive users were compared. Oral contraceptives with specified and unspecified progestogen components were analysed separately. An overall analysis was performed, based on the adjusted odds ratio (OR) and on the 2x2 tables separately. The adjusted ORs were calculated by pooling adjusted ORs from individual studies using a random-effects model. The same method was used for the cohort and case-control studies. Where 2x2 tables were available, the ORs from the individual studies were also combined using the fixed-effect Mantel-Haenszel method (see Other Publications of Related Interest). For subgroup analyses, the adjusted and unadjusted results were pooled because of the limited number of studies with subgroup data, resulting in a pooled OR.

How were differences between studies investigated?
Stratified analyses explored the patterns of risk in subgroups using these factors for stratification: first-time users; age (less than 25 versus at least 25 years); duration of oral contraceptive use (less than 1 year versus at least 1 year); confirmed cases; and source of funding (non-industry versus industry-sponsored studies). Statistical heterogeneity was tested for but the authors do not state which test was used. To determine the stability of the overall risk estimate, a sensitivity analysis was performed in which each study was successively eliminated. The authors also conducted an additional analysis including studies that did not meet the inclusion criteria, to determine their effect on the pooled OR.

Results of the review
Nine case-control studies (n=13,007) and 3 cohort studies (n=1,180,038) comparing second- and third-generation contraceptives, and 3 case-control studies (n=16,891) comparing third-generation and 'other' oral contraceptives, were included in the review.

The overall adjusted OR for third- versus second-generation oral contraceptives was 1.7 (95% CI: 1.4, 2.0; 7 studies). Similar risks were found when oral contraceptives containing desogestrel or gestodene were compared with those containing levonorgestrel. Among first-time users, the OR for third- versus second-generation preparations was 3.1 (95% CI: 2.0, 4.6.; 4 studies). The OR was 2.5 (95% CI: 1.6, 4.1; 5 studies) for short-term users, compared with 2.0 (95% CI: 1.4, 2.7; 5 studies) for longer-term users. The OR was 1.3 (95% CI: 1.0, 1.7) in studies funded by the pharmaceutical industry and 2.3 (95% CI: 1.7, 3.2) in other studies. Differences in age and certainty of the diagnosis of venous thrombosis did not affect the results.

Authors' conclusions
This meta-analysis supported the view that third-generation oral contraceptives are associated with an increased risk of venous thrombosis in comparison with second-generation oral contraceptives. The increase cannot be explained by several potential biases.

CRD commentary
The review question and the study selection criteria were stated clearly. The literature search was limited to MEDLINE and English language literature, which may have led to some studies being missed. Some aspects of study design that could affect validity, such as rigidity of case definitions, were assessed and used in the analysis. Details of the review process, such as how many of the reviewers were involved in selecting the studies, were missing. The study details provided seemed adequate and the pooling method seemed appropriate, although a separate analysis of the case-control and cohort studies would have been preferable.

The authors considered the limitations of observational study designs in their discussion, but these limitations were not
reflected in the conclusions which should, perhaps, have been more cautious.

**Implications of the review for practice and research**

Practice: The authors state that around four deaths per 1,000,000 woman years could be prevented by switching from third- to second-generation products. The risks, although small, should be considered when deciding which oral contraceptive to use.

Research: The authors did not state any implications for further research.

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